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Abstract: Background. Thromboelastometry (ROTEM(R)) might be useful to detect intraoperative coagulation disorders early in major paediatric surgery. This observational trial compares this technique to standard coagulation tests. Methods. Intraoperative blood sampling was obtained in children undergoing elective major surgery. At each time point, standard coagulation tests [activated partial thromboplastin time (aPTT), prothrombin time (PT), and fibrinogen level] and ROTEM(R) analyses (InTEM, ExTEM, and FibTEM) were performed simultaneously by trained hospital laboratory staff. Results. A total of 288 blood samples from 50 subjects were analysed. While there was a poor correlation between PT and aPTT to ExTEM clotting time (CT) and InTEM CT, respectively, a good correlation was detected between PT and aPTT to clot formation time, and a very good correlation between fibrinogen level and FibTEM assay ($r=0.882$, $P<0.001$). Notably, 64% of PT and 94% of aPTT measurements were outside the reference range, while impaired CT was observed in 13% and 6.3%, respectively. Standard coagulation test results were available after a median of 53 min [inter-quartile range (IQR): 45–63 min], whereas 10 min values of ROTEM(R) results were available online after 23 min (IQR: 21–24 min). Conclusions. PT and aPTT cannot be interchangeably used with ROTEM(R) CT. Based on the results of ROTEM(R), recommended thresholds for PT and aPTT might overestimate the need for coagulation therapy. A good correlation was found between the fibrinogen level and the FibTEM assay. In addition, ROTEM(R) offered faster turnaround times.

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Comparison of thromboelastometry (ROTEM®) with standard plasmatic coagulation testing in paediatric surgery

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Editor's key points

- Major surgery can result in significant blood loss and coagulopathy in children requiring rapid and accurate assessment of coagulation status.
- This observational study compared standard coagulation testing to rotational thromboelastometry in children undergoing major surgery.
- Standard coagulation testing did not correlate well with thromboelastometry testing except for fibrinogen levels with FibTEM.
- Further studies are needed to develop thromboelastometry-guided transfusion guidelines in children.

Background. Thromboelastometry (ROTEM®) might be useful to detect intraoperative coagulation disorders early in major paediatric surgery. This observational trial compares this technique to standard coagulation tests.

Methods. Intraoperative blood sampling was obtained in children undergoing elective major surgery. At each time point, standard coagulation tests [activated partial thromboplastin time (aPTT), prothrombin time (PT), and fibrinogen level] and ROTEM® analyses (InTEM, ExTEM, and FibTEM) were performed simultaneously by trained hospital laboratory staff.

Results. A total of 288 blood samples from 50 subjects were analysed. While there was a poor correlation between PT and aPTT to ExTEM clotting time (CT) and InTEM CT, respectively, a good correlation was detected between PT and aPTT to clot formation time, and a very good correlation between fibrinogen level and FibTEM assay ($r=0.882$, $P<0.001$). Notably, 64% of PT and 94% of aPTT measurements were outside the reference range, while impaired CT was observed in 13% and 6.3%, respectively. Standard coagulation test results were available after a median of 53 min [inter-quartile range (IQR): 45–63 min], whereas 10 min values of ROTEM® results were available online after 23 min (IQR: 21–24 min).

Conclusions. PT and aPTT cannot be interchangeably used with ROTEM® CT. Based on the results of ROTEM®, recommended thresholds for PT and aPTT might overestimate the need for coagulation therapy. A good correlation was found between the fibrinogen level and the FibTEM assay. In addition, ROTEM® offered faster turnaround times.

Keywords: blood, coagulation; complication, coagulopathy; measurement techniques, coagulation; measurement techniques, thrombelastograph

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Major surgical procedures in children are frequently associated with significant blood loss per kilogram body weight and the resulting need for transfusion of allogeneic blood products, which can be further aggravated by development of dilutional coagulopathy.¹ As a result, early detection of signs of coagulopathy is a major issue and challenge for paediatric anaesthetists. Standard coagulation tests [prothrombin time (PT), activated partial thromboplastin time (aPTT), and plasma fibrinogen level] in the perioperative setting are time-consuming,² which delays prompt haemostatic therapy.

Rotation thromboelastometry (ROTEM®, TEM® Innovations, Munich, Germany) offers an alternative approach to assess perioperative coagulation disorders by means of visco-elastic analysis of clotting *in vitro*. First results are

available within 10 min of test initiation, and clot formation can be observed online by a bedside monitor. The current recommendations for transfusion of fresh frozen plasma (FFP) or administration of prothrombin complex concentrates are mainly based on prolonged PT and aPTT.⁴ Recently, results in trauma patients show good results using the ROTEM® clotting time (CT) instead of PT/aPTT to assess coagulation status.⁵ Only limited data comparing the two approaches are available.

The aims of the current clinical observational study were (i) to compare standard coagulation measurements (PT, aPTT, and fibrinogen level) with ROTEM® testing and (ii) to compare the times required for performance of each method.

Methods

This prospective observational study project was approved by the institutional Ethics Committee of University Children's Hospital Zurich (KEK StV 27/08). Written informed consent was obtained from parents. The study was performed in paediatric patients undergoing elective major surgery with a high likelihood of considerable blood loss and the need for close intraoperative coagulation testing. Patients were excluded if preoperative standard coagulation tests or blood count were abnormal, or any history of hereditary or acquired coagulopathy including renal, hepatic, and bone marrow disease were known. No uniform transfusion protocol was used, as the main focus was the comparison between both coagulation measurements. Most anaesthetists used classical plasmatic coagulation intervention guidelines,⁴ and some of the younger anaesthetists used ROTEM[®] to monitor fibrinogen concentration.

Blood samples were obtained at baseline in all subjects after general anaesthesia was induced and venous or arterial access was established, and thereafter at the discretion of the anaesthesiologist in charge during the entire surgical procedure. At each time point, two 3 ml tubes containing 0.14 ml citrate solution (S-monovettes[®], Sarstedt, Nuembrecht, Germany) were taken for coagulation and ROTEM[®] tests and immediately transported manually to the hospital central laboratory. All intraoperative measurements were labelled as urgent on the form that was filled in for our laboratory personnel.

Citrated blood of one tube was analysed after centrifugation at 3000g for 15 min at 18°C on a STA Compact[®] coagulation analyser (Roche Diagnostics AG, Rotkreuz, Switzerland) to measure PT, aPTT, and fibrinogen. Simultaneously, thromboelastometry was performed in the hospital central laboratory by trained operators using the ROTEM[®] device. Technical details of the ROTEM[®] analyser have been described elsewhere.⁶ The CT was defined from the start of measurement until the initiation of clotting after 20 µl of a buffered concentrated calcium chloride solution (StarTEM[®] reagent) and the activator was added to the whole blood sample.

To compare measurements of standard coagulation tests (PT, aPTT, and fibrinogen level), the following corresponding ROTEM[®] tests were defined:⁶

- CT and clot formation time (CFT) of the extrinsically activated ROTEM[®] assay (ExTEM CT and CFT, respectively); activation with 20 µl tissue factor to be compared with the PT;
- CT and CFT of the intrinsically activated ROTEM[®] assay (activation of 20 µl phospholipid-ellagic acid; InTEM CT and CFT, respectively); to be compared with the aPTT;
- Comparison of the functional fibrinogen test (Clauss assay) to be compared with the clot firmness after 10 min (FibTEM A10) and to the maximum clot firmness (FibTEM MCF) of the FibTEM assay. The FibTEM test was based on an ExTEM assay that also contains the platelet

inhibitor cytochalasin D to separately evaluate functional fibrin polymerization without platelet activity.

In addition, platelet count was correlated to InTEM and ExTEM maximum clot firmness (MCF) and to the clot amplitude after 10 min (A10).

All devices were set up according to quality standards and underwent periodic quality controls. Immediately after results of standard coagulation measurements were available, the laboratory staff gave a call to the anaesthetist in charge and this time was noted for comparison of time of performance. In contrast, the ROTEM[®] device was connected to an intranet network that allows online display of the resulting curves at the anaesthesia monitoring device. The time was noted when the 10 min results of the ROTEM[®] assays were available online (A10 values).

The SPSS software package (Version 18.0; SPSS Inc., Chicago, IL, USA) was used for statistical analyses. After testing for Gaussian distribution revealed a non-parametric distribution of laboratory data, Spearman's correlation was used for analysis. Data are presented as median values with Q1 and Q3 quartiles if not otherwise noted.

Results

A total of 288 intraoperative coagulation analyses were obtained in 50 subjects undergoing major surgery. Surgical procedures included craniofacial ($n=23$), spine ($n=22$), complex hip ($n=2$), or cancer surgery ($n=3$). Subject characteristics and intraoperative transfusion requirements are presented in Table 1.

Overall correlation of the investigated assays and corresponding reference ranges are shown in Figures 1–3. As the reference ranges for standard coagulation tests and ROTEM[®] measurements are slightly different for each paediatric age group, we used a calculated mean value for displayed reference ranges in Figures 1–3 based on previous published data.^{7,8}

PT showed a poor correlation to the CT of the extrinsically activated ROTEM[®] assay (ExTEM CT) ($r=-0.460$, $P<0.001$), but a high correlation to the CFT (ExTEM CFT; $r=-0.782$, $P<0.001$).

A slightly higher correlation was detected between results of activated partial thromboplastin time (aPTT) and CT and CFT of the intrinsically activated ROTEM[®] test (InTEM), $r=0.723$ ($P<0.001$) and $r=-7.89$ ($P<0.001$), respectively. Surprisingly, 94% of all aPTT values were outside the reference range, and according to the current guidelines, in 52%, prolongation of aPTT was designated to be clinically meaningful (>45 s). In contrast, increase in InTEM CT was only detected in 18 out of 285 analyses (6.3%). Since no conclusive threshold for CT has been published and validated, we defined CT values outside the normal range as abnormal.

The overall correlation of PT and ExTEM CT and of aPTT and InTEM CT was not significantly higher if only levels within the reference ranges were compared (calculations not shown).

Measurements of the functional fibrinogen tests using the Clauss assay and ROTEM[®] FibTEM A10 and MCF showed a

Table 1 Subject characteristics ($n=50$) and description of intraoperative transfusion therapy. Data are expressed as median (IQR) or number, as appropriate

Subject characteristics and intraoperative course	
Age (yr)	3.2 (0.8–10.7)
Gender (female/male)	24/26
Height (cm)	87.2 (72.2–118)
Weight (kg)	13.0 (9.0–22.5)
Total amount of infused crystalloids and colloids (ml kg^{-1})	128 (94.1–167)
Transfusion of RBC (ml kg^{-1}) (in 44 out of 50 patients)	40.0 (20.8–65.1)
Transfusion of FFP (ml kg^{-1}) (in 24 out of 50 patients)	21.9 (11.1–32.3)
Transfusion of platelets (ml kg^{-1}) (in 8 out of 50 patients)	16.7 (12.6–26.6)
Administration of human fibrinogen concentrate (mg kg^{-1}) (in 37 out of 50 patients)	44.5 (16.2–77.0)

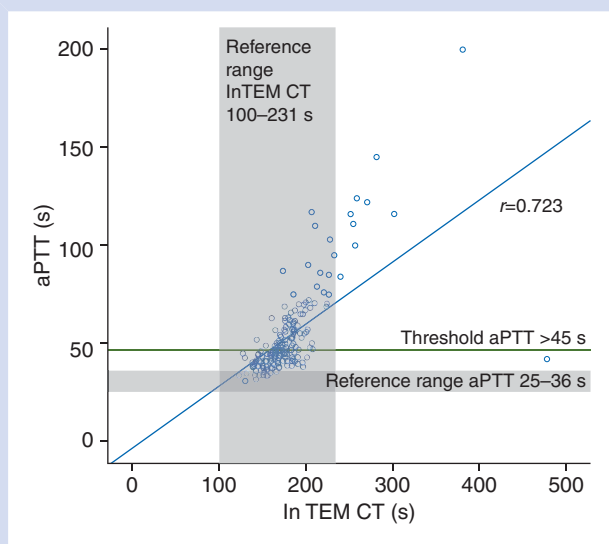


Fig 1 Correlation between ROTEM® InTEM CT and aPTT. Reference ranges are shown for each parameter. Critical threshold for aPTT according to the current guidelines^{4 11} is displayed.

high overall correlation ($r=0.823$, $P<0.001$ and $r=0.882$, $P<0.001$). Both assays revealed impaired fibrin polymerization (FibTEM MCF <7 mm) and diminished plasma fibrinogen levels (Clauss assay <1.8 g litre^{-1}) in about 33% of all intraoperative coagulation analyses.

Clot amplitude A10 and MCF showed a high correlation to platelet count in the InTEM assay ($r=0.9$, $P<0.001$ and $r=0.873$, $P<0.001$, respectively) as well as in the ExTEM test ($r=0.860$, $P<0.001$ and $r=0.77$, $P<0.001$, respectively).

Results of standard coagulation measurements were transmitted immediately by phone call from the central

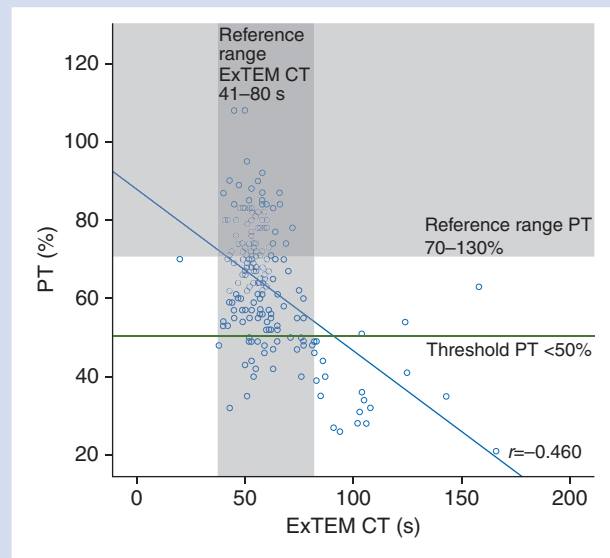


Fig 2 Correlation between ROTEM® ExTEM CT and PT. Reference ranges are shown for each parameter. Critical threshold for PT according to the current guidelines^{4 11} is displayed.

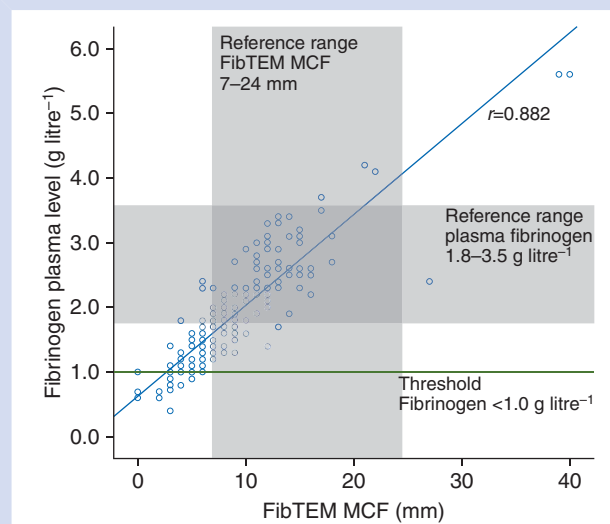


Fig 3 Correlation between ROTEM® FibTEM MCF and plasma fibrinogen level. Reference ranges are shown for each parameter. Critical threshold for plasma fibrinogen level according to the current guidelines⁴ is displayed.

laboratory which took a median of 53 min [inter-quartile range (IQR): 45–63 min] after blood sampling, whereas 10 min values of ROTEM® (A10) were available online after 23 min (IQR: 21–24 min).

Discussion

A major finding of this study is that only a moderate correlation exists between standard coagulation tests such as PT

or aPTT compared with the CTs using the extrinsically or intrinsically activated ROTEM[®] tests. Similar findings of only modest correlation are supported by results of other study groups.^{7 9 10} Therefore, results of CT in ROTEM[®] tests and results of PT or aPTT cannot be used interchangeably for detecting intraoperative haemostatic disorders.

While impaired CT values were observed in only X% (37 out of 285 samples), more than 64% of PT measurements were outside the reference range (185 out of 288). PT values below a threshold of 50 s were observed in 22.6%. Impaired activation of the extrinsic pathway was uniformly detected with both assays in 37 out of 288 samples (13%). Even more surprisingly, 94% of all aPTT values were outside the reference range; and according to the current guidelines, in 52%, prolongation of aPTT levels was classified as clinically meaningful (>45 s).¹¹ In contrast, increase in InTEM CT was only detected in 18 out of 285 analyses (6.3%). This difference between tests might be explained by the fact that standard coagulation tests are performed in plasma while ROTEM[®] tests use whole blood. Apart from that, PT/aPTT measurements depend on the reagents used, incubation time, and the method of endpoint detection and show considerable variability between laboratories.

Tripodi and colleagues¹² stated that standard coagulation tests failed to reflect the balance between the actions of pro- and anticoagulant factors. Another aspect is that children in our study experienced different stages of dilutional coagulopathy, which is likely to be differently displayed by various coagulation measurements.

Notably, InTEM and ExTEM CFT showed a fairly high correlation to aPTT and PT, respectively. This was in accordance with the results from adult trauma patients that showed an excellent correlation between InTEM CFT and aPTT ($r=0.91$), while correlation between InTEM CT and aPTT was rather poor ($r=0.47$).⁹ Despite a good correlation between clot strength after 15 min (ExTEM CA15) and PT in that investigation, the question of the optimal threshold for laboratory coagulation testing and ROTEM[®] measurements that reliably guides adequate haemostatic therapy remains. Recommendations of critical thresholds for PT and aPTT in current guidelines were based largely on expert opinion and sparse publications of clinical studies.^{13–15} The PT or aPTT tests have been shown to overestimate the underlying coagulation factor activity if more than one factor is reduced,¹⁶ which typically occurs in dilutional coagulopathy. Thus, impaired aPTT or PT values are a very common and early finding during intraoperative bleeding and haemodilution.^{15 17} If these early abnormalities are not linked to relevant increase in bleeding, this might lead to considerable over-transfusion of FFP and other blood products. In adult liver transplantation, Wang and colleagues¹⁸ showed a significant decrease in transfused allogeneic blood products following a transfusion algorithm using ROTEM[®] compared with standard laboratory tests. Data from Schöchl and colleagues revealed the effective use of ROTEM[®]-guided coagulation management in trauma patients by reducing the amount of allogeneic blood product transfusion.⁵ However, there is a lack

of data proving the usefulness of ROTEM[®]-guided coagulation management in children.^{19 20}

Clot firmness analysed A10 or at maximum levels showed a very good correlation to platelet count. This finding is supported by data from liver transplantation in adults providing similar results ($r=0.779$, $P<0.001$).²¹ Thus, MCF or even A10 values might serve as surrogate parameters to estimate platelet function.

Fibrinogen/fibrin is an important contributor to clot strength and is the first coagulation factor to become critically reduced during perioperative haemorrhage and dilutional coagulopathy.^{17 22 23} In our study, plasma fibrinogen level assessed with the Clauss assay showed a high to a very high correlation to the FibTEM A10 and MCF. This finding is supported by other studies showing similar good correlations.^{9 24} Impaired functional fibrinogen levels were observed in our study considerably more frequently based on the Clauss assay (54%), while the FibTEM MCF showed impaired values in 37% of test results. Severe deterioration of plasma fibrinogen levels below 1.0 g litre^{-1} were observed in 11%. Although a minimum level of plasma fibrinogen of 1 g litre^{-1} was recommended by older guidelines^{4 25}, there is growing evidence that considerably higher fibrinogen levels ($>1.5\text{--}2 \text{ g litre}^{-1}$) are necessary to control bleeding.^{26–31} However, no universal threshold for minimum fibrinogen levels is supported by evidence-based data, and this could depend on other factors such as the type of surgery or concomitant coagulation factor activities. Another meaningful limitation of the Clauss assay is that fibrinogen levels can be considerably altered after massive fluid resuscitation and that colloids can induce erroneously increased levels of fibrinogen when using the photometric Clauss method.^{28 32} Recently published data suggest that the mechanical detection principle of fibrinogen testing is more reliable than photometric techniques.³³

Overall, there was a clear advantage for ROTEM[®] compared with standard coagulation tests in their shorter turnaround times, which will have an impact on timely and more targeted coagulation therapy.^{19 24 28 34 35} Although point-of-care testing devices for the measurement of PT and aPTT might improve the time delay of standard laboratory testing, the other limitations of standard testing in the perioperative setting were still valid.

Some limitations in our study design need to be mentioned. First, ROTEM[®] analyses were performed not as bedside tests but in a central laboratory with a certain time delay for sample transport. However, previous studies using the ROTEM[®] have shown that blood samples remain stable over time.³⁶ Secondly, gelatin solution was exclusively used for fluid resuscitation in the majority of children, but not following a uniform strategy; thus, it was not possible to distinguish the impact on coagulation measurements from other causes for coagulopathy. Finally, this study was not designed to compare laboratory findings with clinical signs of increased bleeding. As a matter of course, transfusion therapy was not solely based on laboratory findings but additionally related to clinical observations. Difficulties in

distinguishing surgical from coagulopathic bleeding might increase the likelihood of more liberal transfusion regimens. Furthermore, a normal ROTEM[®] trace showed a high negative predictive value and might identify surgical bleeding early by distinguishing it from coagulopathic bleeding.³⁷ More effort to evaluate and standardize intraoperative visual assessment of coagulopathic bleeding in combination with coagulation measurements is required.

In conclusion, PT and aPTT cannot be used interchangeably to predict ROTEM[®] CT. Based on the results of ROTEM[®] testing, the currently recommended thresholds for PT and aPTT might overestimate the need for coagulation therapy. A good correlation was found between fibrinogen levels and the FibTEM assay. In addition, ROTEM[®] offers faster turnaround times, which can impact on timely monitoring and guiding coagulation therapy.

Conflict of interest

T.H. has received speaker fees and travel support from CSL Behring GmbH and Octapharma AG.

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